A better, safer clot buster for heart attacks, strokes and other cardiovascular diseases

A clot that obstructs blood flow triggers the onset of most heart attacks and 85% of strokes, the leading causes of death and disability worldwide. Reestablishing blood flow rapidly limits damage to the heart or brain, saves lives, and restores well-being. Since “time is heart or brain,” treatment should be initiated rapidly, meaning pre-hospitalization.

A “clot busting” drug, or thrombolytic, is the only therapy able to fulfill this requirement by dissolving the clot with a simple injection. A thrombolytic is different from a “blood thinner” or anticoagulant, which is a drug that prevents clots from forming but cannot dissolve or lyse them. Anticoagulants have evolved and improved significantly over the years, whereas the same thrombolytic, called tissue plasminogen activator or tPA, has been used for over thirty years, despite its shortcomings.

As a result, tPA has recently been replaced, not by another thrombolytic, but by a catheterization procedure, angioplasty. Although hospital-based and time-consuming, angioplasty has out-performed tPA and is now the treatment of choice for heart attacks. In stroke, tPA is used in only about 5% of patients because of its limited efficacy and risk of brain hemorrhage in 6-7% of patients treated.

tPA is part of the body’s natural thrombolytic system that controls the size of “good” blood clots needed to stop bleeding, and which is involved in the repair of “wear and tear” injuries of blood vessels. In this system, tPA is remarkably effective, in contrast to its relatively poor efficacy in therapy. This discrepancy is explained by the presence of the other thrombolytic, urokinase plasminogen activator or uPA, in the natural system.

In nature, tPA’s function is limited to initiating thrombolysis by dissolving the first 33% of the clot. The remaining 66% is lysed by uPA. Since most uPA is carried on the surface of certain blood cells, it has often escaped detection and the importance of its thrombolytic function has gone unrecognized.

The natural design of tPA and uPA, however, shows they were intended to function in combination and not alone. In combination, their clot dissolution effect becomes strongly synergistic, which means that the combined effect is greater than the sum of their individual effects. For example, small doses of tPA and uPA that induce 25% clot lysis by each, induce 100% lysis when they are combined.

A similar sequential combination was tested clinically in 101 patients with heart attacks given a small initial injection of tPA followed by an infusion of uPA. The coronary vessel responsible for the attack was opened in 82% of patients, there were 1% deaths, and no bleeding [JACC

’95;26:374-79]. By comparison, in the best tPA trial the responsible vessel was opened in only 45% of patients, there were 6.3% deaths, and 1.5% strokes [NEJM ’93;329:673-82]. Therefore, fractional doses of tPA and uPA, i.e. 5% and 40% of their usual doses respectively, had an unprecedented efficacy and safety in combination. This experience validates nature’s thrombolytic paradigm as a model regimen for thrombolytic therapy.

Unfortunately, these results could not be followed up because uPA clinical development was abandoned. This was because when uPA was used alone at higher doses, its natural proenzyme state converted to its enzymatic form in blood, which caused bleeding side effects, resulting in a marketing application being turned down.

Therefore, studies to improve uPA’s stability were undertaken. The uPA mutant that was eventually selected is five-fold more stable but retains 99.8% identity with natural uPA and shares its properties. A synergistic combination of a mini-dose of tPA followed by mutant-uPA is a “clot buster” with unprecedented efficacy and safety soon entering clinical trials.

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Publication

Why so little progress in therapeutic thrombolysis? The current state of the art and prospects for improvement.
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